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THE QUANTITATIVE RELATIONSHIPS OF THE PARTITION COEFFICIENTS CALCULATED IN THE SERIES OF N-R-AMINE FUNCTIONAL DERIVATIVES

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Key words: partition coefficient; calculation methods; correlation; N-R-amine derivatives

Using on-line services and the ChemBioOffice2014 software package the values of the partition coefficients of some N-R-amine derivatives have been calculated. To identify the quantitative relationships and select the optimal algorithm of calculations the correlation and regression analysis of the values obtained has been conducted. Statistically significant values of correlation for the partition coefficients calculated have been determined. It has been shown that it is advisable to use the value AlogPs for further application.

Lipophilicity is one of the criteria for assessing the similarity of synthetic substances and drugs, and it affects the biological activity of substances [9, 13, 14]. The partition coefficient of *n*-octanol-water (logP) characterizes physicochemical properties of substances in solutions and is used to simulate their behaviour in the body [3, 14]. Distribution and redistribution of substances between lipophilic (fatty) and aqueous phases are part of biological processes, in particular transmembrane transport through lipid layers [11]. Hydrophobicity plays an important role in determining distribution of a substance in the body after absorption, its metabolic rate and elimination. The hydrophobic effect is essential for binding of drugs with their receptors [13].

The ability to predict biological properties of compounds through their lipophilicity allows to optimize the search for new drugs and is often included in equations for calculations of the quantitative structure – activity relationships (QSAR) [16].

The value logP is experimentally determined by the classical method of measuring distribution of organic compounds between the non-polar phase and water [14] using chromatographic [18], electrochemical [23] and other methods.

However, experimental methods to determine logP are time-consuming and expensive, and the values obtained often differ due to the influence of many factors. Therefore, today a significant number of algorithms for theoretical calculations of values logP implemented using the appropriate software [5, 6, 8, 17, 24, 25].

The values of the partition coefficients of *n*-octanol-water experimentally obtained with the values theoretically calculated by different algorithms (AlogPs, IALogP, ClogP, miLogP, logP_{K_{ow}WIN}, xlogP3, etc.) were compared for 193 substances [19] and more than 96 000 compounds (including databases of Nycomed and Pfizer) [15]. In both studies the experimental data better correlate with the methods of AlogPs, xlogP3, logP_{K_{ow}WIN}.

Attempts to achieve proportionality of results of the theoretical calculation methods of prediction and the experimental determination of lipophilicity of organic compounds are still relevant in modern scientific studies [1, 16, 22].

The aim of this work is to determine the mutual correlation of the values of the partition coefficients in the series of some functional derivatives of N-R-amines (**1-21**) calculated by different algorithms.

Materials and Methods

Taking into account the data [15, 19] we used the available free on-line methods xlogP3 [25], AlogPs [6] for calculations of the partition coefficients, and the ChemBioOffice2014 software package, in particular ChemBioDrawUltra 14.0 (CBDU14) and ChemBio3DUltra 14.0 (CB3DU14) [7], for calculations of logP and ClogP (Table).

In total, the statistical sample included the comparison of 6 values of the partition coefficients calculated for 21 compounds. During the statistical processing of the research results when analysing the sample with the length of 21 cases the values of the Pearson correlation coefficient, which is more than 0.40 ($p \leq 0.05$), is considered to be statistically significant [2].

Calculations of correlations of the values of the partition coefficients calculated for compounds **1-21** were performed using the STATISTIKA 8 software [4, 21]. According to the requirements of mathematical statistics the correlation coefficient indicates the close relationship between the values: at values less than 0.3 – the relationship is absent, in the range of 0.3-0.7 it is medium, more than 0.7 – it is strong [10, 20].

Results and Discussion

As can be seen from Table, almost all compounds are characterized by negative values of the partition coefficients; probably it is due to the presence of the polar moiety – substituted Nitrogen atom in their structure. Increase of numeric values, and hence lipophilicity, is observed in the case of increase in the number of non-polar substituents (alkyl substituents or the phenyl nucleus in compounds **19-20**). Glycine (**12**), for which the calculated values (excluding logP) agree with the experimental ones [12], and its alkyl substituents (**13, 16**) are characterized by the maximum values of hydrophilicity. It can be also explained by the considerations previously mentioned.

Table

Structures and the values logP calculated of compounds 1-21

No.	Structure	AlogPs	xlogP3	logP CBDU14	logP CB3DU14	ClogP CBDU14	ClogP CB3DU14
1	<chem>N</chem>		-0.73			-1.2	-1.2
2	<chem>CCN</chem>	-1.06	-0.71	-0.65	-0.57	-0.664	-0.664
3	<chem>CCCN</chem>	-0.2	-0.35	-0.32	-0.32	-0.135	-0.135
4	<chem>OCCN</chem>	-1.53	-1.31	-1.17	-1.31	-1.295	-1.295
5	<chem>CN(C)N</chem>	-0.53	-0.20	-0.13	-0.134	-0.518	-0.518
6	<chem>CCN(C)N</chem>	0.76	0.58	0.54	0.50	0.54	0.54
7	<chem>OCCN(C)N</chem>	-1.41	-1.43	-1.17	-1.43	-1.463	-1.463
8	<chem>CN(C)C</chem>	-0.14	0.26	0.24	0.27	0.018	0.018
9	<chem>CCN(C)C</chem>	1.57	1.45	1.26	1.44	1.605	1.605
10	<chem>OCCN(C)C</chem>	-1.38	-1.00	-1.31	-2.218	-1.228	-1.228
11	<chem>C[N+](C)(C)C</chem>	-1.59	0.28			-4.856	-4.856
12	<chem>NC(=O)O</chem>	-3.34	-3.21	-1.39	-3.0	-3.210	-3.210
13	<chem>NC(=O)O</chem>	-3.24	-3.73	-0.97	-2.296	-2.811	-2.811
14	<chem>NC(=O)O</chem>	-1.76	-3.60	-0.97	-3.293	-1.742	-1.742
15	<chem>NC(=O)O</chem>	-1.94	-1.30			-3.747	-3.747
16	<chem>NC(=O)O</chem>	-3.06	-2.78	-0.87	-1.275	-3.124	-3.124
17	<chem>NC(=O)O</chem>	-1.70	-2.91	-0.49	-0.6	-2.368	-2.368
18	<chem>NC(=O)O</chem>	-1.90	-0.13			-4.173	-4.173
19	<chem>NC(=O)O</chem>	1.39	1.26	1.5	1.5	0.224	0.224
20	<chem>NC(=O)O</chem>	-0.32	-0.93	1.24	1.24	-0.600	-0.600
21	<chem>NC(=O)O</chem>	-1.40	1.37			-1.755	-1.755

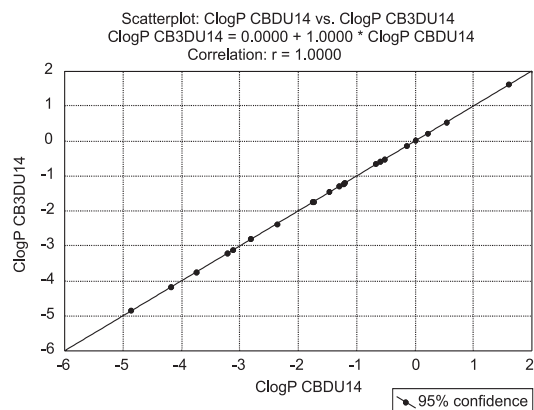


Fig. 1. Correlation of ClogP CBDU14 and ClogP CB3DU14.

Analysis of the results of statistical processing indicates that the coefficients of lipophilicity calculated by different algorithms for compounds (1-21) correlate (%) with each other in a different way and are statistically significant (Fig. 1-11).

It can be noted that the algorithms for calculating logP in ChemBioDrawUltra 14.0 and ChemBio3DUltra 14.0 do not allow to determine a numeric value for ionic compounds (11, 18, 21), and compounds that do not contain Carbon atoms (in our case NH_3 – compound 1) (Table). The latter is observed for calculation of AlogPs. It should also be noted that the values ClogP calculated by Chem BioDrawUltra 14.0 and ChemBio3DUltra 14.0 are absolutely the same ($r = 1.000$) unlike the values logP similarly obtained where the correlation is slightly less ($r = 0.91745$) (Table, Fig. 1, 2).

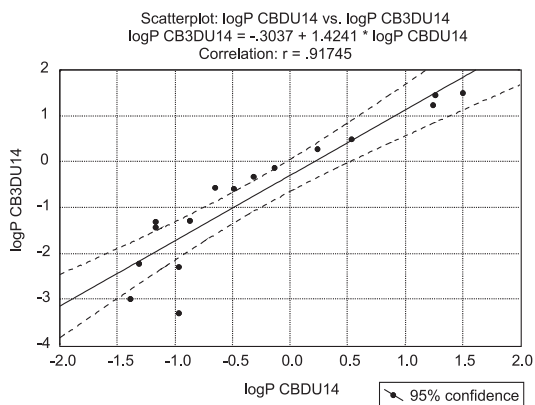


Fig. 2. Correlation of logP CBDU14 and logP CB3DU14.

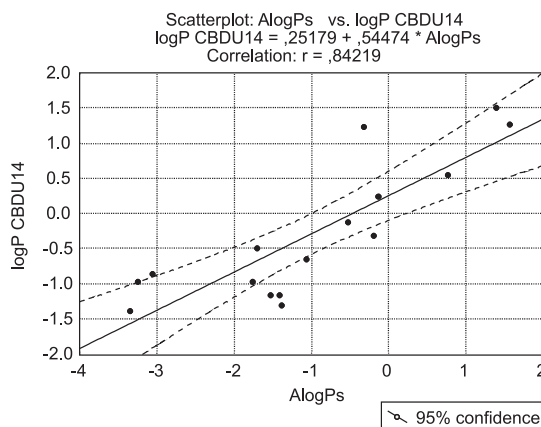


Fig. 4. Correlation of AlogPs and logP CBDU14.

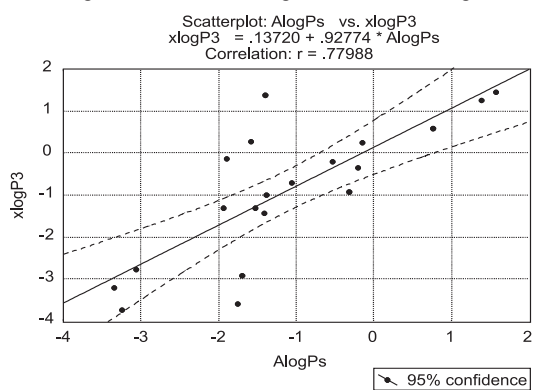


Fig. 3. Correlation of AlogPs and xlogP3.

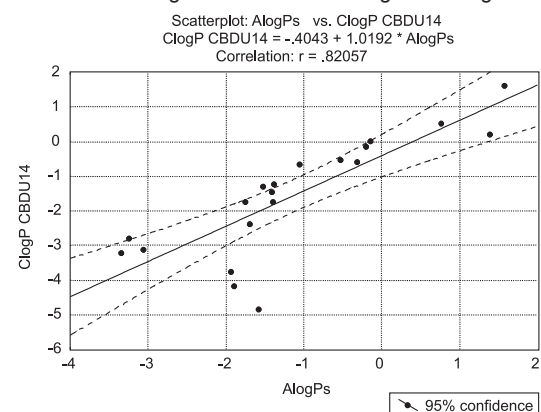


Fig. 6. Correlation of AlogPs and ClogP.

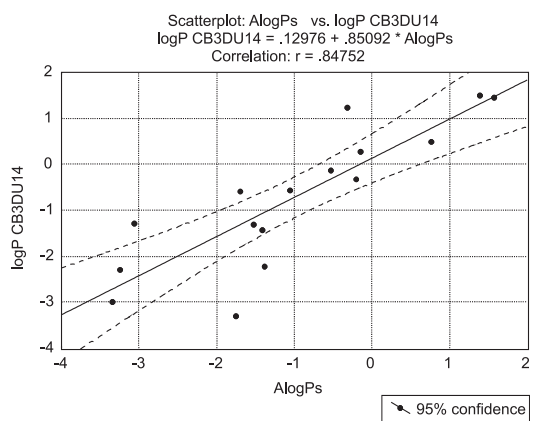


Fig. 5. Correlation of AlogPs and logP CB3DU14.

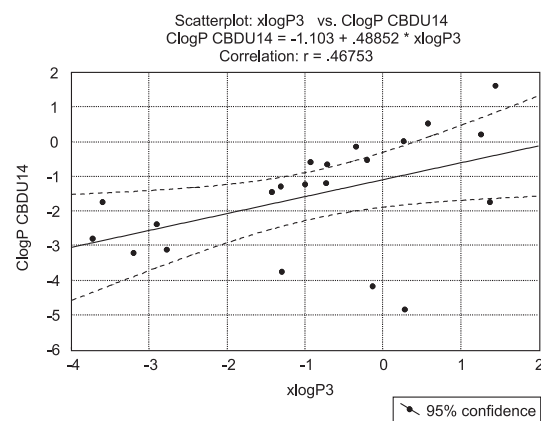


Fig. 8. Correlation of xlogP3 and ClogP.

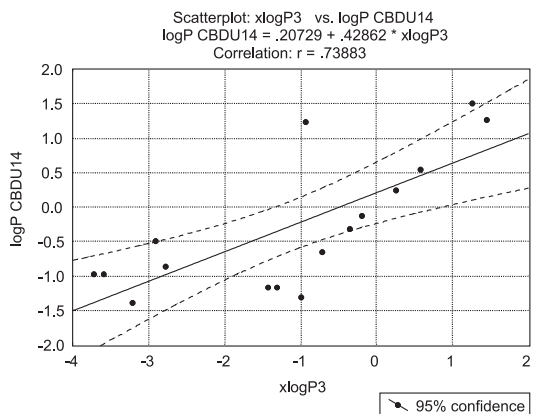


Fig. 7. Correlation of xlogP3 and logP CBDU14.

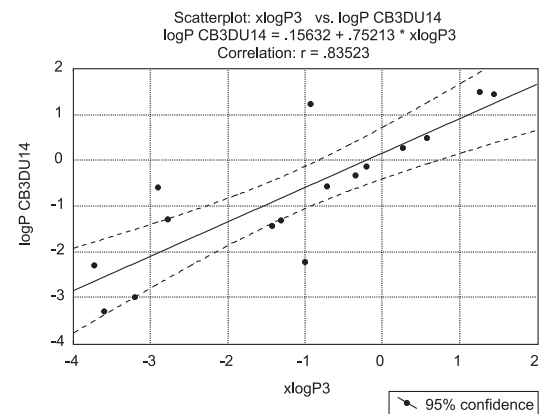


Fig. 9. Correlation of xlogP3 and logP CB3DU14.

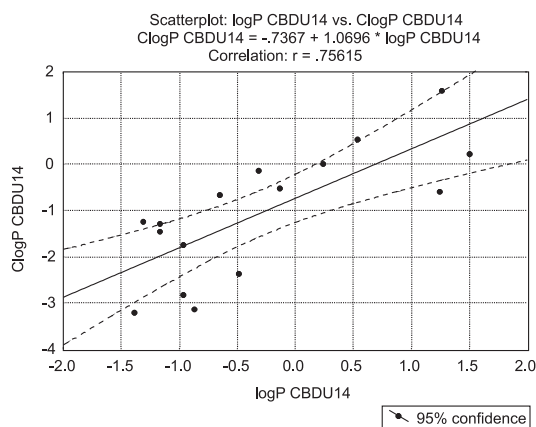


Fig. 10. Correlation of logP CBDU14 and ClogP.

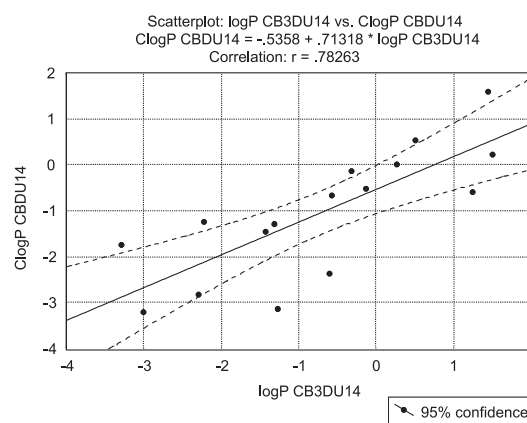


Fig. 11. Correlation of logP CB3DU14 and ClogP.

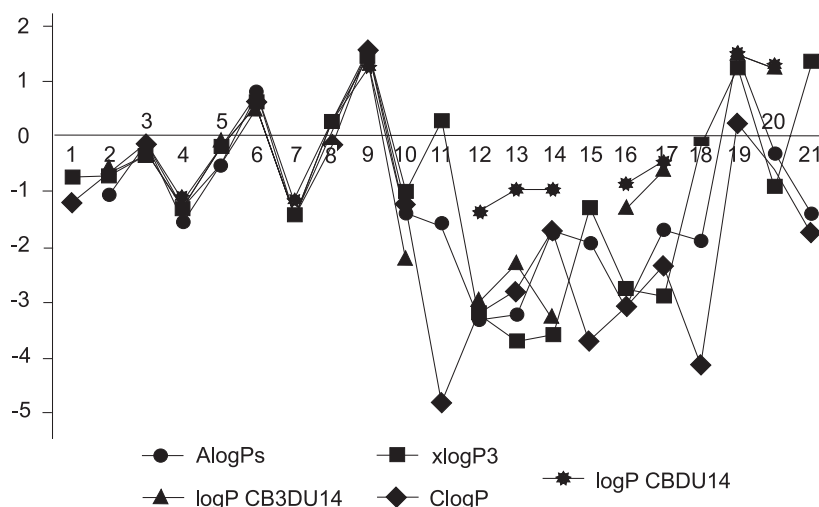


Fig. 12. The relationship of values of the partition coefficients calculated by different algorithms.

The maximum values of correlations that are consistent with the published data [15, 19] are observed in cases of AlogPs and logP CBDU14 ($r = 0.84219$), as well as AlogPs and logP CB3DU14 ($r = 0.84752$) (Fig. 4, 5, respectively). Somewhat smaller values are in the cases of xlogP3 and logP CB3DU14 ($r = 0.83523$) (Fig. 9), as well as AlogPs and ClogP ($r = 0.82057$) (Fig. 6). The minimum correlation was in the case of xlogP3 and ClogP ($r = 0.46753$) (Fig. 8). Other combinations occupied the intermediate values within the range of 73-78%: AlogPs and xlogP3 ($r = 0.77988$), xlogP3 and logP CBDU14 ($r = 0.73883$), logP CBDU14 and ClogP ($r = 0.75615$), logP CB3DU14 and ClogP ($r = 0.78263$) (Fig. 3, 7, 10, 11).

These combinations of the Pearson correlation coefficients and indicators of significance indicate the reliability of the graphs and equations shown in Fig. 1-11.

The position of the curve the values AlogPs theoretically calculated in relation to the results of other calculations of the partition coefficients (Fig. 12) may in-

dicate the use of the optimally averaged algorithm of their determination.

Therefore, the results of our study allow to propose the values AlogPs obtained for further application when determining QSAR, as well as the degree of its manifestation among N-R-amine derivatives for planning a targeted search biologically active substances in this series.

CONCLUSIONS

1. Using on-line services and the ChemBioOffice2014 software package the values of the partition coefficients of some N-R-amine derivatives have been calculated.

2. To identify the quantitative relationships and select the optimal algorithm of calculations the correlation and regression analysis of the values obtained has been conducted.

3. Statistically significant values of correlation for the partition coefficients calculated have been determined. It has been shown that it is advisable to use the value AlogPs for further application.

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КІЛЬКІСНІ СПІВВІДНОШЕННЯ РОЗРАХОВАНИХ КОЕФІЦІЄНТІВ РОЗПОДІЛУ У РЯДУ ФУНКЦІОНАЛЬНИХ ПОХІДНИХ N-R-АМІНІВ

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Ключові слова: коефіцієнт розподілу; розрахункові методи; кореляція; N-R-амінопохідні
З використанням он-лайн сервісів та програмного пакету ChemBioOffice2014 розраховані значення коефіцієнтів розподілу деяких N-R-амінопохідних та з метою виявлення кількісних співвідношень і вибору оптимального алгоритму розрахунків проведено кореляційно-регресійний аналіз одержаних значень. Встановлені статистично достовірні значення кореляції розрахованих коефіцієнтів розподілу та показано, що для подальшого використання доцільно використовувати значення AlogPs.

КОЛИЧЕСТВЕННЫЕ СООТНОШЕНИЯ РАССЧИТАННЫХ КОЭФФИЦИЕНТОВ РАСПРЕДЕЛЕНИЯ В РЯДУ ФУНКЦИОНАЛЬНЫХ ПРОИЗВОДНЫХ N-R-АМИНОВ

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Ключевые слова: коэффициент распределения; расчетные методы; корреляция; N-R-аминопроизводные

При использовании он-лайн сервисов и программного пакета ChemBioOffice2014 рассчитаны значения коэффициентов распределения некоторых N-R-аминопроизводных и с целью выявления количественных соотношений и выбора оптимального алгоритма расчетов проведен корреляционно-регрессионный анализ полученных значений. Установлены статистически достоверные значения корреляции рассчитанных коэффициентов распределения и показано, что для дальнейшего использования целесообразно использовать значение AlogPs.